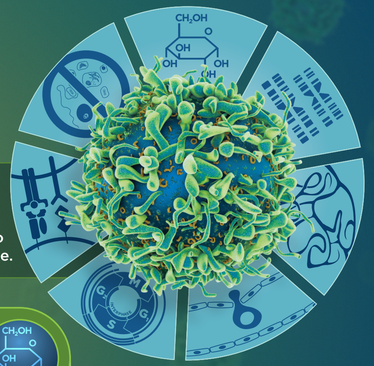
Beyond the Hallmarks:

Mechanisms of Cancer's Genesis and Persistence

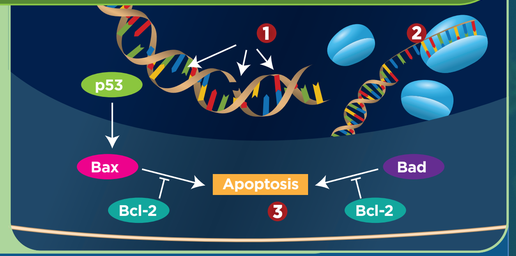
The journey of a healthy cell through oncogenesis and tumorigenesis involves the activation and inactivation of numerous mechanisms and processes–acute and chronic, cellular and systemic. Understanding how cancer alters physiological homeostasis and hijacks integral innate mechanisms for its own benefit is critical to the conception and development of novel therapeutic strategies against the disease.



Resistance to Stress and Cell Death

Cancer cells face numerous malignant growth-associated stresses (e.g., hypoxia, DNA damage, and nutrient scarcity) that can impact survival. Adaptive mechanisms allow tumors to compensate for these stresses, bypassing the standard checks that prevent cellular immortality, facilitating tumor formation and growth, and circumventing apoptotic death.[6]

1. Dysfunctional DNA repair mechanisms in cancer allow increased mutagenesis[6]
2. Telomerase upregulation prevents terminal differentiation and senescence[3,6]
3. Cancer cell Bcl-2 family protein expression, p53 mutations, and increased autophagy can confer resistance to stress-induced apoptosis[3,6]

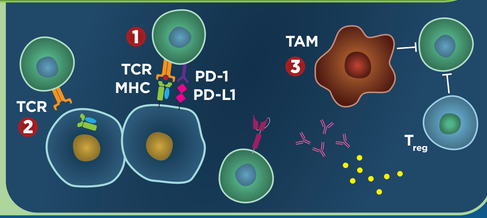


Restoration of normal apoptotic signaling can potentially induce cancer cell death

Immune Modulation

The immune system is designed to identify and eliminate cancer cells prior to tumorigenesis. For cancer cells to proliferate and thrive, they must circumvent or deactivate the immune mechanisms designed to remove them via processes collectively termed "immune evasion."[10]

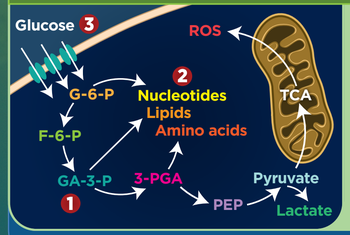
1. Cancer cells can deactivate immune effector cells by triggering regulatory signaling pathways on the immune cell
2. They can avoid immune detection by ceasing to be antigenic
3. The tumor microenvironment promotes regulatory and immunosuppressive immune cell phenotypes[10]



Immunotherapy harnesses and modifies natural mechanisms *(e.g., cytokine and antibody therapy, CAR-T cells)* to counter these tactics.

Metabolic Reprogramming

The tumor microenvironment features conditions that are not amenable to normal cell health. Cancer cells alter their energetics to favor survival and proliferation in this harsh new environment, giving them a competitive advantage over healthy cells.[3]



1. Cancer cells favor aerobic glycolysis over cellular respiration
2. The aerobic glycolysis pathway promotes synthesis of nucleotides, lipids, and amino acids
3. Oncogenes can reprogram cell metabolism to increase nutrient uptake

Cellular metabolic changes promote mutagenesis and cancer progression[3]

Invasion and Metastasis

The formation of secondary tumors in distant locations makes cancer treatment exponentially more difficult, and is a leading reason for cancer morbidity and mortality.[1] Preventing or limiting metastasis is therefore integral to treatment success.[1,2]

1. Cancer cells dissociate from the tumor mass and proteolytically degrade local extracellular matrix to invade the surrounding stroma
2. The invading cell enters and migrates through the lymphatic or circulatory system
3. The circulating cell extravasates at a new location, potentially forming a secondary tumor
4. Factors key to facilitating this process, including endothelial permeability, lymphangiogenesis, and tumor cell proteolytic activity, represent potential therapeutic targets[1,3]

Genome Instability, Mutation, & Epigenetic Modifications

Cancer cells accumulate numerous and varied genetic and epigenetic alterations during oncogenesis and tumorigenesis. This genomic instability confers a heterogeneity that complicates detection and elimination by innate or clinical mechanisms.[4] Disruption of epigenetic processes can lead to altered gene function and malignant transformation.

1. Oncogenesis can develop as a result of mutations in oncogenic genes, oncogene suppressing genes, or epigenetic modifications
2. Chromosomal-level mutations can result in telomere attrition, triggering breakage-fusion-bridge cycles; nucleotide-level mutations can cause repair defects, leading to hypermutation
3. Epigenetic processes (e.g., DNA methylation, histone modifications) can alter gene function leading to malignant cellular transformation
4. Epigenetics detection assays and next-generation sequencing allow researchers to quantify genomic instability beyond simply the number of mutations present[4]

Angiogenesis and Altered Microenvironment

Cancer cell interactions with other cells in the tumor microenvironment (TME), orchestrate stromal cell migration, matrix remodeling, and vascular network expansion. Stromal and vasculature modifications play an integral role in facilitating tumor development and metastasis. The normalization of these aspects can therefore potentially limit tumor growth.[5]

1. Cancer induces cytokine, chemokine, growth factor, and protease secretion by non-cancer cells in the TME (e.g., fibroblasts, adipose cells, lymphatic cells, endothelial cells)
2. Excessive production of VEGF and ANG2 causes abnormal vascular development[3,5] resulting in immature vessels with poor flow and excessive permeability[5]
3. Abnormal vasculature further promotes an altered, hypoxic TME, which in turn stimulates additional angiogenesis[3,5]
4. Combining cancer-directed therapeutics with TME-targeting treatments aims to limit tumor progression and suppress pro-cancer TME mechanisms

Altered Growth Signals and Response

Cancer cells proliferate uncontrollably because of resistance to anti-growth signals and chronically active pro-growth signals.[3,7] Additionally, self-renewing tumorigenesis-capable cancer stem cells (CSCs) have been identified within tumor cell populations.[8]

1. The cell cycle is normally tightly regulated: exogenous growth signals bring cells out of G_0 and both internal and external cues halt proliferation[3,7]
2. Cancer cells deregulate pro-growth signaling pathways, disrupt intracellular anti-growth effectors (e.g., pRb), and downregulate anti-growth pathway receptors (e.g., TGFβ)[3,7]
3. CSC self-renewal (e.g., via Hh, Notch, or Wnt signaling) can be autonomously driven or be promoted by stromal cells[8,9]
4. CSCs can resist chemo- and radiotherapy by remaining in G_0 phase, accumulating mutations over time facilitating malignant transformation[8,9]

REFERENCES

1. M. Yilmaz, et al., "Distinct mechanisms of tumor invasion and metastasis," *Trends Mol Med* 13(12):535-541, 2007.
2. T.A. Martin, et al., "Cancer Invasion and Metastasis: Molecular and Cellular Perspective," In: *Madame Curie Bioscience Database* [Internet]. Austin (TX): Landes Bioscience; 2000-2013. Available from: https://www.ncbi.nlm.nih.gov/books/NBK164700
3. Y.A. Fouad and C. Aanei, "Revisiting the hallmarks of cancer," *Am J Cancer Res* 7(5):1016-1036, 2017.
4. J.K. Lee, et al., "Mechanisms and Consequences of Cancer Genome Instability: Lessons from Genome Sequencing Studies," *Annu Rev Pathol* 11:283-312, 2016.
5. P. Carmeliet and R.K. Jain, "Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases," *Nat Rev Drug Discov* 10(6):417-427, 2011.
6. V. Labi and M. Erlacher, "How cell death shapes cancer," *Cell Death Dis* 6(3): e1675, 2015.
7. D. Hanahan and R.A. Weinberg, "The hallmarks of cancer," *Cell* 100(1):57-70, 2000.
8. A. Borah, et al., "Targeting self-renewal pathways in cancer stem cells: clinical implications for cancer therapy," *Oncogenesis* 4:e177, 2015.
9. C.A. O'Brien, et al., "Cancer stem cells and self-renewal," *Clin Cancer Res* 16(12):3113-3120, 2010.
10. D.S. Vinay, et al., "Immune evasion in cancer: Mechanistic basis and therapeutic strategies," *Semin Cancer Biol* 35 Suppl:S185-S198, 2015.

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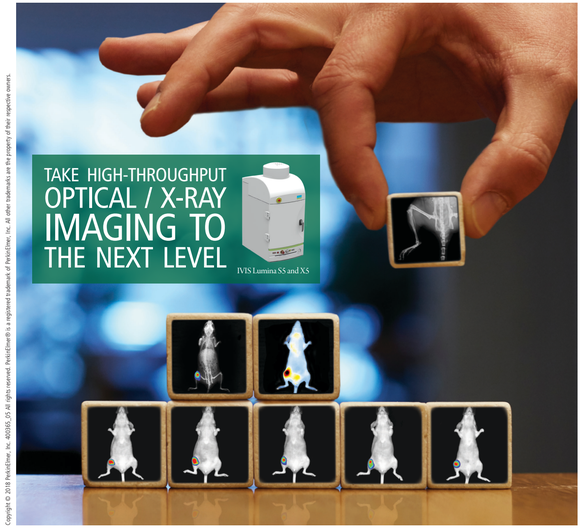

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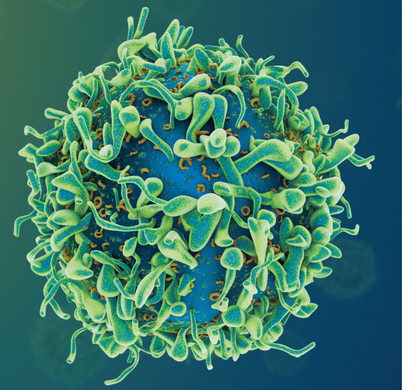

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